Polysomnographic study of the effect of melatonin on sleep in elderly patients with chronic primary insomnia

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Abstract

The effect of 3-mg melatonin capsules p.o. on sleep in ten elderly patients suffering from chronic primary insomnia was assessed by polysomnographic recordings. In general, melatonin significantly reduced wake time after sleep onset and increased total sleep time and sleep efficiency during the 2-week treatment period. In five of the ten patients treated with melatonin, the increase in total sleep time was clinically significant. Side effects were absent during the period of drug administration. A slight increase of power density in the delta and the theta regions was found during the early phase (i.e. nights 4–5) of melatonin administration, whereas the opposite changes were observed at a late phase of treatment (i.e. nights 15–16). No strict correlation was found between prior 6-sulphatoxymelatonin levels in urine and subsequent sleep improvement after receiving melatonin. Our results further support the proposal that melatonin is beneficial for sleep disturbances in elderly insomniacs. © 1999 Elsevier Science Ireland Ltd. All rights reserved.

Keywords: Elderly patients; Primary chronic insomnia; Sleep; Melatonin; 6-Sulphatoxymelatonin; Polysomnography

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1. Introduction

Chronic insomnia by convention is defined as a sleep disturbance that lasts for at least 21–30 nights. Usually it persists for months or years, and its onset may or may not be associated with an identifiable stressor (Consensus Conference, 1984; American Psychiatric Association, 1994). In elderly patients, chronic insomnia can be associated with inappropriate sleep hygiene, psychophysiological conditions (also called primary insomnia), neurological disorders such as dementia or Parkinson’s disease, mental disorders, and drug dependency. The most prevalent diagnosis is chronic insomnia associated with psychiatric disorders, followed in precedence by primary insomnia (Buysee et al., 1994).

Age-related changes in the retina, the suprachiasmatic nuclei, and the pineal gland may be relevant causes for primary insomnia in the elderly, along with behavioral changes such as a reduction in physical activity and in exposure to photic activity. Accordingly, neuronal degeneration at the suprachiasmatic nucleus (Mirmiran et al., 1992) and decreases in the number of pinealocytes (Humbert and Pévet, 1991) and in the amplitude of melatonin rhythms (Iguchi et al., 1982; Skene et al., 1990; Ferrari et al., 1996) have been reported as consequences of aging. Other factors that vary according to circadian rhythms, such as body temperature, physical activity, and the secretion of cortisol, are also altered with aging (Copinschi and Van Cauter, 1995; Myers and Badia, 1995; Touitou, 1995).

In the treatment of primary insomnia, both non-pharmacological strategies and sleep-promoting medication are indicated. Benzodiazepine hypnotics and two compounds that are structurally unrelated to the benzodiazepines (zopiclone, zolpidem) are currently used for the treatment of chronic insomnia in the elderly (Monti and Monti, 1995). One promising therapeutic agent for sleep-disturbed elderly patients is melatonin. Among elderly people, sleep disorders are frequently associated with an impairment of melatonin production (Iguchi et al., 1982; Skene et al., 1990; Haimov et al., 1994; Ferrari et al., 1996), and, as recently reviewed by Sack et al. (1997) and Zhdanova et al. (1997), melatonin can have a beneficial effect on sleep disorders in old age. For example, Haimov et al. (1995) has reported that melatonin replacement therapy in melatonin-deficient elderly insomniacs with a 2-mg sustained-release melatonin preparation was effective for sleep maintenance, while sleep initiation was improved by a fast-release melatonin preparation. After cessation of treatment, sleep quality deteriorated.

Melatonin is secreted into the systemic circulation by the pineal gland, where it is distributed into tissue and biological fluid. In vitro experiments with [^H]-melatonin added to human plasma indicate that 61–78% of melatonin is reversible bound to albumin (Cardinali et al., 1972). Albumin-bound melatonin is readily dissociable and therefore transportable through the blood–brain barrier (Pardridge and Mietus, 1980). Moreover, following its intravenous administration, [^11C]-melatonin is rapidly visualized in the brain of man, which further supports its passage through the blood–brain barrier (Le Bars et al., 1991).

The aim of the present study was to determine the effect of short- and intermediate-term melatonin (3 mg p.o.) administration on sleep in elderly patients with
chronic primary insomnia by means of polysomnographic recordings. 6-Sul-
phatoxymelatonin levels in urine samples taken immediately before treatment were
also measured to determine relevance to treatment outcome. The dose of 3 mg
melatonin produces peak plasma levels that are at least ten times physiologic
concentrations (Sack et al., 1997). Thus, it can be considered a ‘pharmacological
dose’, and tentatively enough to benefit elderly patients with low endogenous levels
of the neurohormone.

2. Materials and methods

2.1. Subjects

The study was a placebo–drug–placebo investigation of ten elderly insomniac
patients (eight females and two males, aged between 66 and 86 years) with chronic
primary insomnia (persistent psychophysiological insomnia) according to DSM-IV
(1994). Detailed information on the patients is presented in Table 1. Patients with
poor health; acute or chronic pain; hepatic, renal, respiratory, cardiac or neuropsy-
chiatric diseases; known drug allergy or abuse; nocturnal myoclonus; restless legs;
or sleep apnea were excluded from the study, as also were subjects deemed
insufficiently compliant. Alcohol abuse or intake of hypnotics or anxiolytics in the
7 days prior to the baseline period also led to exclusion. None of the patients had
been treated with antidepressants or antipsychotics prior to entering the study.

Patients were instructed to refrain from napping and to avoid using any
treatment than could interfere with melatonin secretion, including β-adrenoceptor
blockers and nonsteroidal anti-inflammatory drugs. Caffeine-containing beverages

<table>
<thead>
<tr>
<th>Patient</th>
<th>Gender</th>
<th>Age</th>
<th>Duration of insomnia (years)</th>
<th>Total wake time (min)</th>
<th>Pre-study urinary 6-sulphatoxymelatonin levels (mcg/12 h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Female</td>
<td>73</td>
<td>22</td>
<td>95.5</td>
<td>1.89</td>
</tr>
<tr>
<td>2</td>
<td>Male</td>
<td>67</td>
<td>5</td>
<td>271.5</td>
<td>0.90</td>
</tr>
<tr>
<td>3</td>
<td>Female</td>
<td>79</td>
<td>0.6</td>
<td>172.5</td>
<td>7.20</td>
</tr>
<tr>
<td>4</td>
<td>Female</td>
<td>75</td>
<td>15</td>
<td>276.0</td>
<td>3.32</td>
</tr>
<tr>
<td>5</td>
<td>Female</td>
<td>86</td>
<td>0.7</td>
<td>136.0</td>
<td>1.0</td>
</tr>
<tr>
<td>6</td>
<td>Female</td>
<td>66</td>
<td>6</td>
<td>165.5</td>
<td>37.0</td>
</tr>
<tr>
<td>7</td>
<td>Male</td>
<td>66</td>
<td>21</td>
<td>174.5</td>
<td>22.1</td>
</tr>
<tr>
<td>8</td>
<td>Female</td>
<td>75</td>
<td>2.5</td>
<td>200.5</td>
<td>21.9</td>
</tr>
<tr>
<td>9</td>
<td>Female</td>
<td>73</td>
<td>15</td>
<td>111.0</td>
<td>5.75</td>
</tr>
<tr>
<td>10</td>
<td>Female</td>
<td>86</td>
<td>1</td>
<td>120.0</td>
<td>0.62</td>
</tr>
</tbody>
</table>

$\bar{x} \pm \text{S.E.M.}$ 74.6 ± 2.3 8.9 ± 2.7 172.3 ± 19.8 10.2 ± 4.0
and alcohol were also banned. The following drugs had previously been taken by the patients for insomnia: flunitrazepam \( (t_{1/2} = 20 \text{ h}) \) 1–2 mg \((n = 1)\), midazolam \( (t_{1/2} = 1.2 \text{ h}) \) 15 mg \((n = 1)\), bromazepam \( (t_{1/2} = 18 \text{ h}) \) 3 mg \((n = 2)\), lorazepam \( (t_{1/2} = 15 \text{ h}) \) 1 mg \((n = 1)\), zopiclone \( (t_{1/2} = 6 \text{ h}) \) 7.5 mg \((n = 1)\) and zolpidem \( (t_{1/2} = 2.5 \text{ h}) \) 5–10 mg \((n = 2)\). Administration of the anxiolytic and hypnotic derivatives was gradually reduced. This reduction was well tolerated by all patients, as shown by the absence of withdrawal symptoms. All medication was discontinued at least 7 days before the start of the baseline period. As is well known, once steady state has been achieved, it takes five half-lives for more than 90% of a drug to be eliminated from the body after drug dosing has been discontinued. Considering the short to intermediate half-lives of the sedative/hypnotics taken by the patients prior to entering the study, a 7-day washout period seemed appropriate.

The protocol was reviewed and approved by the institutional Ethics Review Committee, and the patients gave informed consent.

2.2. Design of the study

The period of observation lasted 19 nights and included a total of 9 nights in the sleep laboratory. On the first night placebo was administered to 13 subjects, so that they could adjust to the laboratory and could be screened for the presence of sleep apnea or periodic limb movements, either of which would warrant exclusion from the study. Three subjects were excluded: two because of the diagnosis of sleep apnea and one due to the diagnosis of nocturnal myoclonus. On the next two nights (nights 2 and 3) placebo was again administered to ten subjects single-blind, and sleep was recorded and quantified so that the nature and extent of the sleep disturbances could be estimated. For the succeeding 14 nights, patients were given melatonin orally, single-blind. Subjects slept in the laboratory on nights 4 and 5 (used for analysis of short-term effectiveness) and on nights 15 and 16 (to determine intermediate-term efficacy). On nights 6–14 the medication was taken at home. Placebo was again administered, single-blind and patients slept in the laboratory on nights 17 and 18 to evaluate any withdrawal effects. On the nights when patients attended the sleep laboratory, polygraphic sleep recordings were made for 8 h by means of frontal, parietal and occipital leads, right and left electrooculography and chin electromyography. In order to conform to each patient habitual sleep period, the sleep recordings were started at either 22:30 or 23:30 h. A bedtime earlier or later than the usual one could artificially modify sleep latency or disturb sleep throughout the night.

The sleep records were coded and scored blind. The following variables were scored: non-REM (NREM) sleep latency (from lights out to the first spindle during the first 5 min of stage 2); total wake time; waking time after sleep onset; number of awakenings; total sleep duration; sleep efficiency; and duration of sleep stages 1, 2, 3, and 4; movement time; REM sleep latency (from the first spindle during the first 5 min of stage 2 to REM sleep onset); duration of REM sleep; and number of REM periods.
Identical gelatin capsules of placebo or immediate-release melatonin 3 mg were given daily just before turning off the lights.

In the laboratory mornings, the patients were interviewed about the quality of their sleep and the presence of side-effects. Neither the patients nor the physicians who performed the medical interviews were aware of the treatment (placebo or melatonin) administered. Subjective efficacy measures included estimates of the time required to fall asleep (1, within 30 min; 2, between 31 and 45 min; 3, between 46 and 60 min; 4, more than 60 min); duration of sleep (1, less than 4 h; 2, 4–6 h; 3, 7–8 h); number of awakenings (1, no interruption of sleep; 2, one–two awakenings; 3, three–six awakenings; 4, seven or more awakenings); sleep quality (1, undisturbed; 2, disturbed); and condition on awakening (1, calm and refreshed; 2, tired; 3, sleepy).

Urine was collected for 12 h (from 18:00 to 06:00 h) on the day preceding the adaptation to the sleep laboratory. Samples were frozen at $-20^\circ$C until measurement of urinary 6-sulphatoxymelatonin by RIA (Arendt et al., 1985).

The intra- and the inter-assay coefficients of variation were 6 and 11%, respectively.

2.3. Data analysis

Each sleep record was scored for the variables listed above according to the criteria of Rechtschaffen and Kales (1968). The mean values of each variable for placebo baseline, period of melatonin administration, and placebo (melatonin withdrawal) nights were tested by performing a one-way ANOVA with multiple measures. If the overall $F$-values were significant, the Newman-Keuls post hoc procedure was used to detect the statistical significance of differences between melatonin and placebo.

In addition, one EEG signal (C4-A1) was filtered, digitized at a sampling of 128 Hz, and saved to optical disk. A time code was also written every 20 s on both the paper tracing and the disk. Time code delimited epochs enabled precise correspondence between the visual scoring of sleep records and the computer analysis. Epochs containing artefacts in the EEG lead were eliminated from the analysis. Data saved to optical disk corresponding to NREM sleep episodes were analyzed off-line for consecutive 0.25 Hz bands in the range of 0.25–30 Hz, with PASS PLUS (Delta Software, St. Louis, USA) spectral analysis software (Uchida et al., 1994).

3. Results

The patients included in the study exhibited during baseline nights the sleep EEG features described in elderly insomniacs. Thus, the sleep spindles that characterize stage 2 appeared less frequently, and were often poorly formed, of lower amplitude, and of slower frequency. In addition, the delta waves that characterize stage 3 and stage 4 were greatly attenuated in amplitude.
Fig. 1. Effect of melatonin (3 mg) on the mean EEG power density of NREM sleep (relative to baseline) during an 8-h period. The curves relate mean values ($n = 10$) for successive 1 Hz bins which are expressed as a percentage of the placebo reference value ($= 100\%$), during nights 3–4 (short-term administration period), 15–16 (intermediate-term administration period), and 17–18 (withdrawal period). Differences were not significant as compared to baseline placebo nights.
Table 2
Sleep induction and continuity measures of elderly insomniac patients treated with melatonin a

<table>
<thead>
<tr>
<th></th>
<th>Baseline Nights 2–3</th>
<th>Melatonin Nights 4–5</th>
<th>Melatonin Nights 15–16</th>
<th>Withdrawal Nights 17–18</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 2 sleep latency (min)</td>
<td>32.3 ± 4.1</td>
<td>30.9 ± 5.6</td>
<td>27.8 ± 4.2</td>
<td>36.7 ± 5.6</td>
</tr>
<tr>
<td>Total number of awakenings</td>
<td>30.9 ± 4.6</td>
<td>29.8 ± 5.1</td>
<td>29.3 ± 4.5</td>
<td>29.0 ± 4.8</td>
</tr>
<tr>
<td>Number of awakenings (less than 4 min duration)</td>
<td>22.2 ± 4.6</td>
<td>22.6 ± 4.9</td>
<td>22.6 ± 4.7</td>
<td>20.7 ± 4.6</td>
</tr>
<tr>
<td>Number of awakenings (4 min duration or more)</td>
<td>8.7 ± 0.8</td>
<td>7.2 ± 0.6</td>
<td>6.7 ± 0.7</td>
<td>7.2 ± 0.9</td>
</tr>
<tr>
<td>Total wake time (min)</td>
<td>172.3 ± 19.8</td>
<td>132.2 ± 16.7*</td>
<td>129.0 ± 18.8*</td>
<td>149.5 ± 16.3</td>
</tr>
<tr>
<td>Wake time after sleep onset (min)</td>
<td>144.3 ± 19.3</td>
<td>103.7 ± 15.9**</td>
<td>107.3 ± 15.4**</td>
<td>116.6 ± 15.8</td>
</tr>
<tr>
<td>Total sleep time (min)</td>
<td>306.7 ± 19.7</td>
<td>345.9 ± 16.7**</td>
<td>349.2 ± 18.6**</td>
<td>328.8 ± 16.1</td>
</tr>
<tr>
<td>Sleep Efficiency (%)</td>
<td>63.9 ± 4.1</td>
<td>72.1 ± 3.5*</td>
<td>72.7 ± 3.9**</td>
<td>68.6 ± 3.4</td>
</tr>
<tr>
<td>Movement time (min)</td>
<td>1.0 ± 0.3</td>
<td>1.9 ± 0.5</td>
<td>1.8 ± 0.5</td>
<td>1.7 ± 0.4</td>
</tr>
</tbody>
</table>

a Mean ± S.E.M. for ten patients. Compared to baseline:
* p<0.05;
** p<0.03 (Newman–Keuls test).

During baseline nights increases were observed in stage 2 sleep latency, the number of nocturnal awakenings, total wake time, and wake time after sleep onset, whereas NREM sleep time was found to be reduced in the patients with a complaint of insomnia relative to that of healthy aged individuals (Spiegel, 1981; Vitiello and Prinz, 1994). Stages 3 and 4 (slow wave sleep) were absent, as might have been expected in elderly insomniacs.

Tables 2 and 3 summarize the effects of 3 mg of melatonin p.o. on sleep induction, sleep continuity and on NREM and REM sleep.

Stage 2 sleep latency and the number of awakenings of less or more than 4-min duration were not significantly modified during either, the short- or the intermediate-term administration period. On the other hand, the total wake time and the

Table 3
NREM sleep and REM sleep measures of elderly insomniac patients treated with melatonin a

<table>
<thead>
<tr>
<th></th>
<th>Baseline Nights 2–3</th>
<th>Melatonin Nights 4–5</th>
<th>Melatonin Nights 15–16</th>
<th>Withdrawal Nights 17–18</th>
</tr>
</thead>
<tbody>
<tr>
<td>NREM sleep time (min)</td>
<td>229.7 ± 14.1</td>
<td>253.5 ± 12.6</td>
<td>260.2 ± 14.7</td>
<td>246.2 ± 13.4</td>
</tr>
<tr>
<td>Stage 1 sleep (min)</td>
<td>39.7 ± 4.8</td>
<td>41.5 ± 3.8</td>
<td>43.7 ± 5.7</td>
<td>39.6 ± 5.5</td>
</tr>
<tr>
<td>Stage 2 sleep (min)</td>
<td>190.0 ± 11.6</td>
<td>212.0 ± 12.0</td>
<td>216.5 ± 13.7</td>
<td>206.6 ± 13.6</td>
</tr>
<tr>
<td>REM sleep (min)</td>
<td>77.0 ± 7.5</td>
<td>92.4 ± 5.3</td>
<td>89.0 ± 6.8</td>
<td>82.6 ± 6.1</td>
</tr>
<tr>
<td>REM sleep (% total sleep time)</td>
<td>25.1 ± 1.5</td>
<td>26.7 ± 0.9</td>
<td>25.4 ± 1.5</td>
<td>27.1 ± 1.5</td>
</tr>
<tr>
<td>REM sleep latency (min)</td>
<td>65.1 ± 14.6</td>
<td>74.7 ± 15.5</td>
<td>59.0 ± 12.5</td>
<td>63.3 ± 11.5</td>
</tr>
<tr>
<td>Number of REM periods</td>
<td>3.9 ± 0.3</td>
<td>4.4 ± 0.3</td>
<td>3.9 ± 0.2</td>
<td>3.7 ± 0.2</td>
</tr>
</tbody>
</table>

a Mean ± S.E.M. for ten patients. Differences from baseline were not significant.
Fig. 2. Effect of melatonin (3 mg) on subjective sleep parameters. Mean values for the 10 patients are shown. With the exception of sleep duration, in all other measures lower score means a more positive response. As compared to baseline, melatonin administration did not significantly modify subjective sleep parameters.

Wake time after sleep onset were significantly decreased (Table 2). The total sleep time and the improvement in sleep efficiency were related to larger amounts of NREM and REM sleep. During the withdrawal period, total sleep time and sleep efficiency tended to revert to control levels.

In regard to stage 1, stage 2, and REM sleep, no significant changes were observed during the melatonin administration period.

The effect of melatonin on EEG power density in NREM sleep is shown in Fig. 1. The values of the short-term (nights 3–4), and intermediate-term (nights 15–16) melatonin nights, and of the withdrawal period (nights 17–18) are expressed for each frequency bin relative to the corresponding value of the placebo nights (100%). The spectrum computed for stages 1, 2, 3 and 4 (NREM sleep) of the 8-h recording period revealed an increase of power density in the low frequency range (δ = 0.25–3 Hz; θ = 4–7 Hz) during nights 3–4. However, values did not differ significantly from the placebo levels (repeated measures ANOVA: df = 3; p < 0.1). Moreover, the relative EEG power density revealed a decrease in the delta, theta and sigma (13–15 Hz) bands during nights 15–16. However, comparison of power in corresponding bins revealed no significant treatment effects (repeated
Table 4
6-Sulphatoxymelatonin levels and wake time after sleep onset in elderly insomniacs treated with melatonin*a

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Urinary 6-sulphatoxymelatonin levels (mcg/12 h)</th>
<th>Wake time after sleep onset (min)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Baseline</td>
<td>Short-term</td>
</tr>
<tr>
<td>10</td>
<td>0.62</td>
<td>98.5</td>
<td>132.0 ( + 33.5)</td>
</tr>
<tr>
<td>2</td>
<td>0.90</td>
<td>248.0</td>
<td>141.5 ( - 106.5)</td>
</tr>
<tr>
<td>5</td>
<td>1.0</td>
<td>111.5</td>
<td>42.5 ( - 69.0)</td>
</tr>
<tr>
<td>1</td>
<td>1.89</td>
<td>74.0</td>
<td>73.5 ( - 0.5)</td>
</tr>
<tr>
<td>4</td>
<td>3.32</td>
<td>251.5</td>
<td>209.5 ( - 42.0)</td>
</tr>
<tr>
<td>9</td>
<td>5.75</td>
<td>99.5</td>
<td>83.0 ( - 16.5)</td>
</tr>
<tr>
<td>3</td>
<td>7.20</td>
<td>123.0</td>
<td>54.5 ( - 68.5)</td>
</tr>
<tr>
<td>8</td>
<td>21.90</td>
<td>158.0</td>
<td>66.5 ( - 91.5)</td>
</tr>
<tr>
<td>7</td>
<td>22.10</td>
<td>127.0</td>
<td>123.0 ( - 4.0)</td>
</tr>
<tr>
<td>6</td>
<td>37.00</td>
<td>151.5</td>
<td>111.0 ( - 40.5)</td>
</tr>
</tbody>
</table>

*a Values are the means for each patient during baseline (nights 2–3) and during short-term (nights 4–5) and intermediate-term (nights 15–16) melatonin administration. Differences from baseline values are in parentheses.

measures ANOVA: df = 3; p < 0.09–0.07). All-night EEG power spectra in the theta band corresponding to nights 17–18 also showed a decrease, but differences were not significant as compared to placebo nights (repeated measures ANOVA: df = 3; p < 0.1).

Subjective evaluation of the ten patients included in the study showed no correlation with sleep laboratory findings (Fig. 2). In four patients in whom melatonin induced a clinically significant increase of total sleep time, however the subjective ratings of the duration of sleep were improved (p < 0.03). No side-effects were reported by the patients during the melatonin administration period.

Table 5
Total sleep time (in min) in responders and non-responders after melatonin administration to elderly insomniac patients*a

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Baseline</th>
<th>Short-term</th>
<th>Intermediate-term</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>381.5</td>
<td>384.5 ( + 3.0)</td>
<td>366.0 ( - 15.5)</td>
</tr>
<tr>
<td>2</td>
<td>207.0</td>
<td>331.5 ( + 124.5)</td>
<td>337.5 ( + 130.5)</td>
</tr>
<tr>
<td>3</td>
<td>306.0</td>
<td>366.0 ( + 60.0)</td>
<td>397.0 ( + 91.0)</td>
</tr>
<tr>
<td>4</td>
<td>204.0</td>
<td>240.0 ( + 36.0)</td>
<td>233.5 ( + 29.5)</td>
</tr>
<tr>
<td>5</td>
<td>342.0</td>
<td>422.5 ( + 80.5)</td>
<td>409.0 ( + 67.0)</td>
</tr>
<tr>
<td>6</td>
<td>313.0</td>
<td>320.0 ( + 7.0)</td>
<td>400.0 ( + 87.0)</td>
</tr>
<tr>
<td>7</td>
<td>306.0</td>
<td>311.0 ( + 5.0)</td>
<td>263.0 ( - 43.0)</td>
</tr>
<tr>
<td>8</td>
<td>279.0</td>
<td>389.0 ( + 110.0)</td>
<td>349.0 ( + 70.0)</td>
</tr>
<tr>
<td>9</td>
<td>369.0</td>
<td>379.0 ( + 10.0)</td>
<td>387.0 ( + 18.0)</td>
</tr>
<tr>
<td>10</td>
<td>359.0</td>
<td>315.0 ( - 44.0)</td>
<td>350.0 ( - 9.0)</td>
</tr>
</tbody>
</table>

*a Values are the means in minutes. Differences from baseline values are in parentheses.
A strict correlation between pre-study 6-sulphatoxymelatonin levels and sleep improvement after melatonin administration could not be established. Accordingly, in three patients (#1, #9 and #10) who had very low urine levels of the melatonin metabolite, wake time after sleep onset, a variable that reflects the continuity of sleep, showed almost no change. In contrast, wake time after sleep onset was markedly decreased in two patients (#6 and #8) where 6-sulphatoxymelatonin levels were in the range observed in adults with normal sleep (±20–30 mcg/12 h) (Table 4). Table 5 shows that in four (#2, #3, #5, #8) of the ten patients treated with melatonin, the increase in total sleep time during nights 4–5 and 14–15 was large enough to be clinically significant (range 60.0–130.0 min). The benefit of the neurohormone on sleep in a fifth patient (#6) was restricted to nights 14–15 (mean increase of 87.0 min).

4. Discussion

A major finding of this study shows that melatonin significantly reduced wake time after sleep onset and increased total sleep time and sleep efficiency during the 2-week treatment period. In five of the ten patients treated with melatonin, the increase in total sleep time was clinically significant.

Moreover, the results reported do not support a strict correlation between sleep disorders among elderly patients, and impairment of melatonin production.

We made use of the placebo–drug–placebo design within a single group of subjects to study the effect of melatonin on sleep in elderly insomniac patients.

It has been argued by Roehrs et al. (1990) that a parallel placebo group is necessary to adequately control a study with a placebo–drug–placebo design. As stated by Bixler et al. (1995), however ‘this additional group is not necessary because the objective measurements and rigorous control of multiple variables in the sleep laboratory result in stable values for sleep and wakefulness’. Recently, we reported on a polysomnographic study that included a parallel placebo group (Monti et al., 1996). Across the period of observation, which lasted 12 nights in the sleep laboratory, there were only minor, non-significant, changes in the parallel placebo group in terms of the values of wakefulness, NREM sleep, and REM sleep. On the other hand, the sleep disturbances observed during baseline improved significantly in the group that received a hypnotic drug, and returned to approximately baseline levels during the withdrawal period. This outcome further demonstrates the stability of such polysomnographic data.

It should be noted that clinical trials based on patients’ subjective perceptions of the quality of their sleep always require a large number of subjects. In contrast, a relatively small number of patients studied in the sleep laboratory can provide significant data on the effect of a given pharmacotherapy on sleep variables (Soldatos and Kales, 1979; Bixler and Kales, 1985). Thus, our sample of ten subjects was adequate to determine the effects of melatonin in patients with chronic primary insomnia.
Sleep prior to treatment was markedly disturbed in our group of elderly insomniac patients. The baseline polysomnographic findings indicate that these patients had difficulty falling and staying asleep. In comparison with normals, awakenings were increased in number, and sleep was fragmented. In addition, slow wave sleep was absent. Baseline REM sleep latency and REM sleep time (in min) were moderately reduced, whereas the percentage of REM sleep was within normal levels.

With respect to stage 2 sleep latency and the number of awakenings, the effect of regular (immediate-release) melatonin was not significant and was inconsistent with previously reported data. Thus, Haimov et al. (1995), Wurtman and Zhdanova (1995) found that latency to sleep onset was improved after administration of 2 or 0.3 mg of immediate-release melatonin, respectively. The differences in results could be related to the time of melatonin administration. Accordingly, our patients received melatonin immediately before lights off, whereas in the Wurtman and Zhdanova (1995), Haimov et al. (1995) studies the hormone was administered 30 min and 2 h before bedtime, respectively. Although melatonin is rapidly absorbed after oral administration, peak plasma levels occur only after 0.5–2 h. Thus, in order to obtain a decrease of stage 2 sleep latency, the hormone should be given at least 30 min in advance of the usual bedtime.

Melatonin significantly increased total sleep time and sleep efficiency throughout the 14-night treatment period. Analysis of the data on a patient-by-patient basis showed that a total sleep time increase large enough to be clinically significant (≥ 60 min) was observed only in five out of the ten patients. Improvement in sleep was already evident during the first drug administration night, and no rebound insomnia was observed following the abrupt discontinuation of melatonin. Our results are in agreement with those of Garfinkel et al. (1995), Haimov et al. (1995), who monitored sleep–wake patterns by wrist-worn actigraphs. These authors found an improvement of sleep maintenance and efficiency in elderly insomniacs receiving sustained-release melatonin 1 or 2 mg orally.

The elimination half-life of regular melatonin after exogenous oral doses is 30–50 min; however, mean peak plasma melatonin concentrations range from 750 to 5–10 ng/ml after 1 or 10-mg doses, respectively (Dollins et al., 1994), which tends to indicate that plasma levels well above the physiological ones are to be found 4–6 h after the administration of a 3-mg dose. This could tentatively explain the moderate-to-large increase of total sleep time in the five patients who responded to melatonin administration in the present study.

The absence of a clinically relevant effect in the remaining five patients does not seem to be related to prior nocturnal levels of 6-sulphatoxymelatonin, because four of them showed low or very low levels of the metabolite in urine, while the fifth one had values similar to these occurring in adults with normal sleep.

This lack of correlation is further supported by the sleep improvement after melatonin found in one insomniac patient with high urinary 6-sulphatoxymelatonin excretion.

It should be mentioned that there are two studies of insomniac patients with negative or indeterminate findings. In the study by James et al. (1990) that included
ten patients with chronic insomnia (mean age, 33.4 years), REM sleep latency was increased after 1.0 mg of melatonin, while a 5.0-mg dose improved sleep quality. The absence of a decrease of stage 2 sleep latency could have been a result of the patients taking their medication only 15 min before lights off. Moreover, under placebo conditions the subject population showed a mean total sleep time of 395.0 min and a sleep efficiency of 88%. Thus, the effect of melatonin could have been limited by a ceiling effect.

The study by Ellis et al. (1996) comprised 15 patients with chronic primary insomnia (mean age, 46.0 years) who received 5.0 mg melatonin. Effects on sleep and wakefulness were monitored by a visual analogue scale and a structured interview. It should be noted that the patients’ subjective estimates of sleep quality could have had a large degree of variability because of the influence of recent as well as past experiences with other sleep medications. In addition, the small sample size of the study could have been an obstacle to obtaining adequate power.

The EEG power spectrum has been previously shown to increase in the delta, theta and sigma bands after administration of 5 mg melatonin to young adult subjects. On the other hand, the alpha and the beta bands are significantly decreased (Tzischinsky and Lavie, 1994; Haimov and Lavie, 1997). In the present study a slight but nonsignificant increase of power density in the delta and the theta regions was found during the short-term (nights 4–5) melatonin administration period. On the other hand, the relative EEG power density corresponding to the delta, theta and sigma bands during intermediate-term (nights 15–16) melatonin administration showed a decrease that did not attain significance. Therefore, in contrast to what has been described in young adults, melatonin did not significantly modify low-frequency EEG activity in elderly insomniacs, in whom delta waves are markedly decreased in number and amplitude.

On the whole, subjective evaluation was not correlated with the sleep laboratory findings. Thus, the compound did not improve subjective ratings of the perceived ease of getting to sleep, the duration and quality of sleep and the condition on awakening.

In conclusion, the present and other recent results indicate that the use of melatonin may be beneficial for treating sleep disturbances in elderly persons. It must be noted that clinical studies need to be performed in order to identify possible side effects of long-term melatonin treatment, especially in elderly or diseased subjects.

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References


